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First-in-human study of LY3039478, an Oral Notch signaling inhibitor in advanced or metastatic cancer

Supplementary Data

Definitions

A dose-limiting toxicity was defined as an AE during cycle 1 that is related to LY3039478 and that fulfills any one of the following criteria using the NCI CTCAE v 4.0: ≥3 CTCAE grade 3 nonhematological toxicity (exceptions made for nausea, vomiting, or constipation that lasts <72 hours and can be controlled with treatment; transient grade 3 elevations of alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]), CTCAE grade 4 hematological toxicity of >5 days duration, any febrile neutropenia, grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia, and other significant toxicity deemed to be dose limiting by investigator.

Immunoreactivity for the NICD fragment**:** A case was adjudicated positive for if equal or more than 10% of the tumor cells demonstrated specific nuclear staining with 1+ or greater intensity, based on cutoff established previously for the assay using transfected cell lines, known constitutionally mutationally active cell lines, and cell lines with no known Notch pathway activation to generate NICD fragments recognized by the proprietary IHC reagent antibodies.

List of 18 genes Notch signaling analyzed:

Hairy and enhancer of split-1 (Hes 1), Hes 2, Hes 3, Hes 4, Hes 5, Hes 6, Hes 7, hairy/enhancer of split related with YPRW motif (Hey 1), Hey 2, Hey L, olfactomedin 4 (OLFM 4), atonal bHLH transcription factor 1 (ATOH 1), deltex E3 ubiquitin ligase 1 (DTX1), DTX2, Notch-regulated ankyrin repeat (NRARP), V-MYC Aavian

myelocyomatosis viral oncogene homolog (MYC), V- Myc avian myelocytomatosis viral oncogene neuroblastoma-derived homolog (MYCN), and Cyclin D1 (CCND1).

Supplementary Table 1. Summary of Dose-Limiting Toxicities

Cohort (Dose)	Number of DLTs	Description of DLT	Maximum CTCAE Grade
Cohort 4 (20 mg)	1	Thrombocytopenia with bleeding	4
Cohort 5 (30 mg)	1	Thrombocytopenia with bleeding	4
Cohort 7 (60 mg)	1	Thrombocytopenia	4
Cohort 9 (100 mg)	1	Nausea not manageable with medical treatment, fatigue	3
	1	Colitis	3

Supplementary Table 2. Serious Adverse Events (Possibly Drug-Related), and Discontinuations Occurring in the Dose Confirmation Phase

	Adverse Event	Total (N=55) n (%)
Gastrointestinal	Diarrhea	7 (12.7)
	Colitis	3 (5.5)
	Nausea	2 (3.6)
	Anal Abscess	1 (1.8)
	Rectal Abscess	1 (1.8)
	Vomiting	1 (1.8)
	Hepatocellular Injury	1 (1.8)
Respiratory	Bronchitis	1 (1.8)
	Pulmonary Artery Aneurysm	1 (1.8)
General	Asthenia	2 (3.6)
	Pyrexia	2 (3.6)
	Abdominal Pain	1 (1.8)
	Hypotension	1 (1.8)
	Renal Failure	1 (1.8)
Metabolism Related	Decreased Appetite	1 (1.8)
Skin and Subcutaneous	Squamous Cell Carcinoma	1 (1.8)
	Squamous Cell Carcinoma of Skin	1 (1.8)
Discontinuations due to Study Drug-Related TEAEs	Diarrhea	2 (3.6)
	Nausea	1 (1.8)
	Decrease in Platelet Count	1 (1.8)

Supplementary Table 3. JJCA Mean PK Parameters Following Multiple Oral LY3039478 Doses of 2.5 to 100 mg in part A and B Patients with Intensive PK Sampling

Geometric Mean (%CV)										
Day 22 (Dose #10)										
	Part A								Part B	Part A
	2.5 mg	5 mg	10 mg	20 mg	30 mg	45 mg	60 mg	75 mg	75 mg	100 mg
N[a]	2/2e	3/3	4/3	6/6	5/5	5/5	5/4	4/4	6/4	5/5
t_{max}[b] (h)	1.00-1.00	2.00 (0.33-2.00)	2.00 (1.00-2.00)	2.00 (1.00-4.00)	2.00 (1.00-4.00)	1.00 (1.00-2.03)	1.00 (0.50-2.42)	2.05 (2.00-4.00)	2.00 (0.98-4.00)	1.00 (1.00-2.00)
C_{max} (ng/mL)	23.7-24.1	38.0 (34)	81.9 (87)	175 (28)	191 (60)	522 (28)	516 (57)	444 (55)	531 (38)	770 (72)
$AUC_{(0-48)}$ (ng•h/mL)	92.1-120	290 (33)	585 (90)	1170 (38)	1290 (71)	3220 (57)	2530 (37)	3350 (78)	2750 (25)	3900 (90)
$t_{1/2}$[c] (h)	6.10-6.11	6.32 (6.00-6.74)	5.83 (4.72-6.79)	5.76 (4.64-7.09)	6.03 (5.01-8.35)	5.74 (5.31-7.12)	5.44 (4.62-7.13)	5.19 (4.77-5.54)	4.85 (3.83-5.76)	5.39 (5.04-5.68)
R_A[d] (ratio)	1.58-1.92	1.03 (15)	1.43 (5)	1.10 (16)[g]	0.911 (19)	2.14 (44)[e]	0.972 (12)	0.516-1.20[f]	1.04 (53)	0.789 (71)[g]

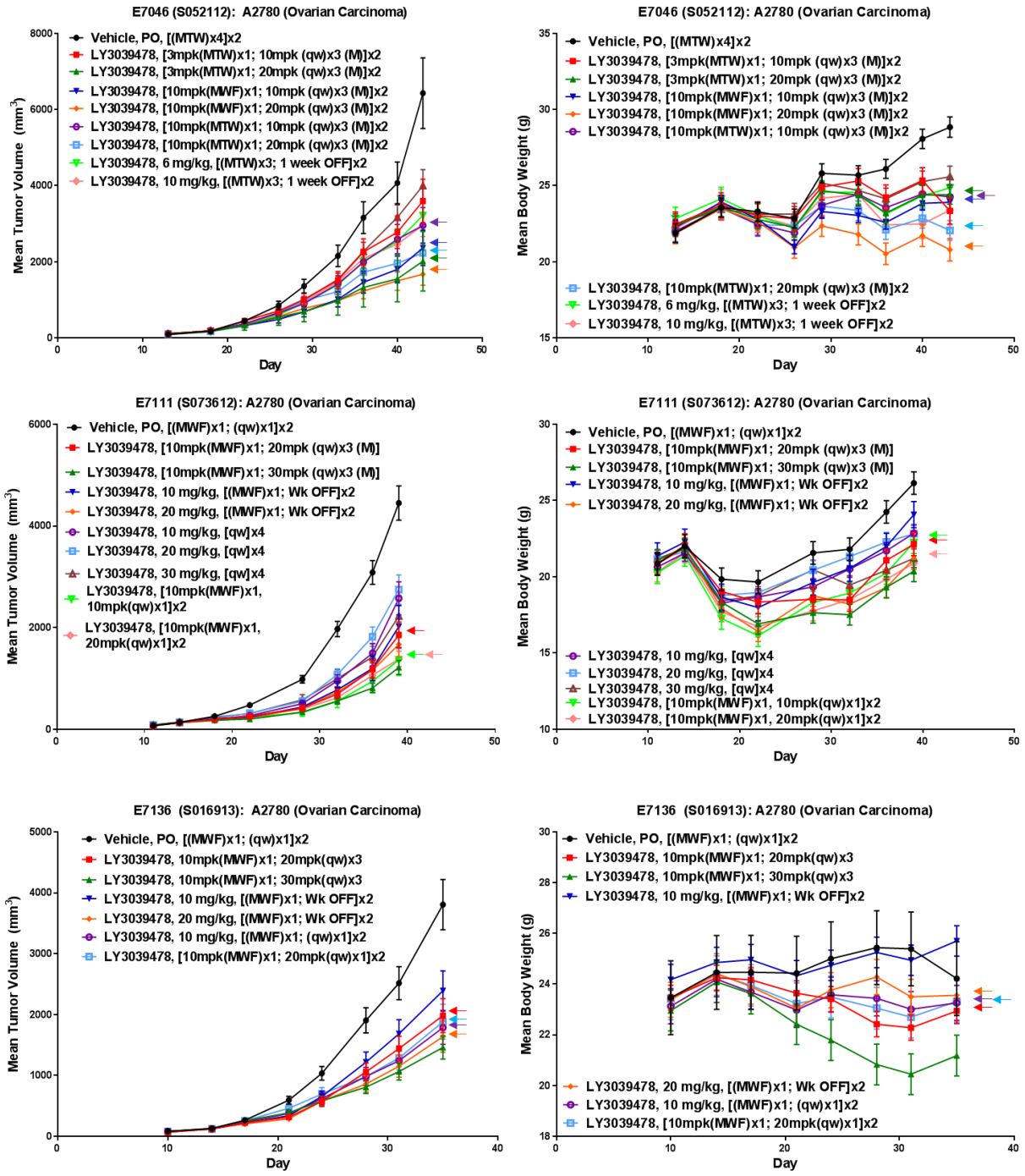
[a] Two N values reported. First N value is for Cmax and tmax, while second N value is for remaining parameters that are dependent on terminal phase of PK profile. Parameters dependent on terminal phase only reported when 24hr time point is available and when $[(AUC_{(0-\infty)}-AUC_{last})/AUC_{0-\infty}]*100 \leq 15\%$.
[b] Median (range)
[c] Geometric mean (range)
[d] Accumulation ratio AUC (0-24) [Day 22]/AUC(0-24) [Day 1]
[e] N=4; one patient's RA not calculated since 75 mg was accidentally administered as Dose #1.
[f] Range reported when N=2.
[g] N=4.

Supplementary Table 4. Mean PK Parameters Following Single Oral LY3039478 Doses of 50 to 75 mg in part B Patients with Sparse PK Sampling

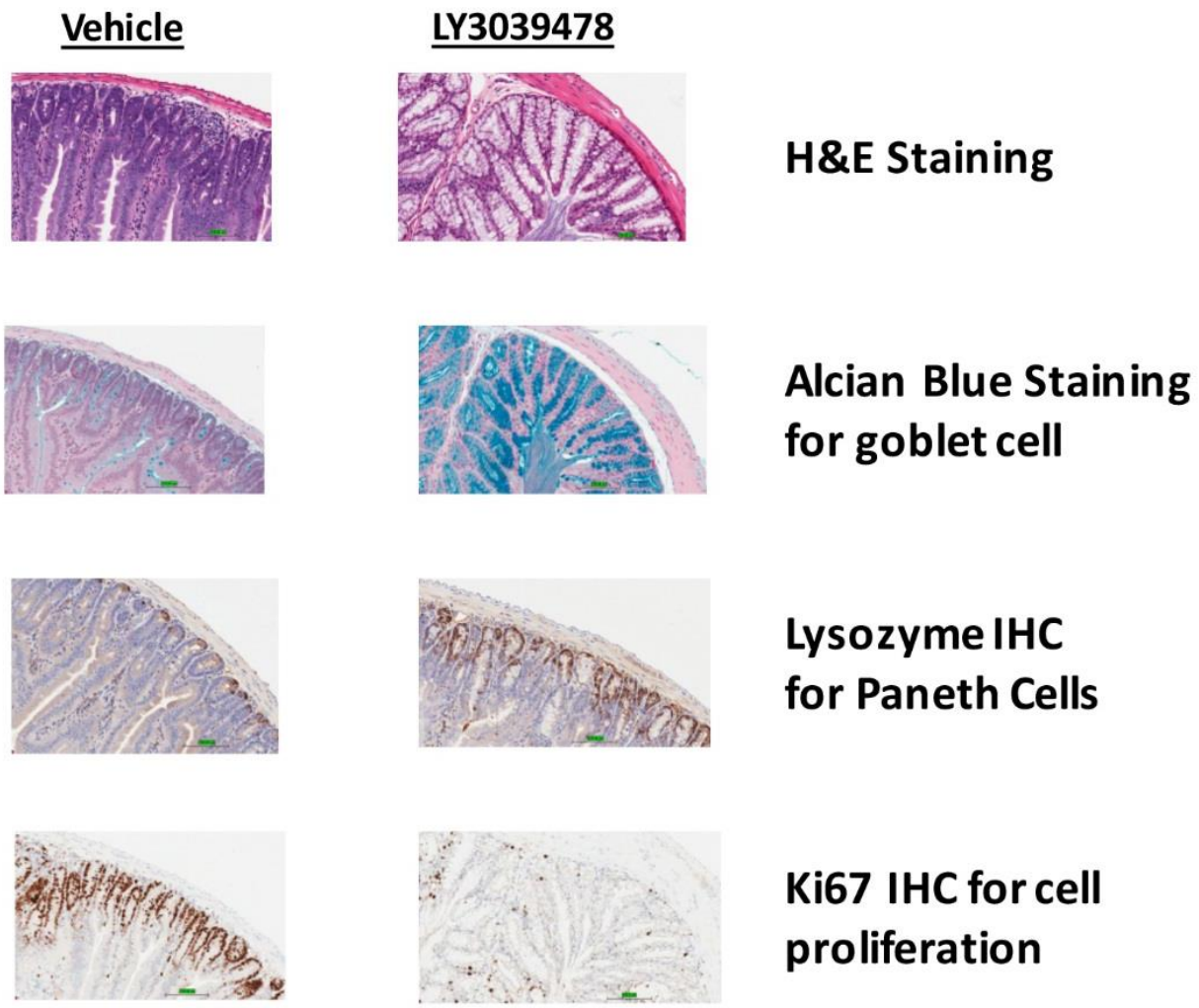
Geometric Mean (%CV)		
Day 1 (Dose #1)		
	50 mg	**75 mg**
N	27	13
t_{max}[a] (h)	2.00 (0.50-4.00)	1.92 (1.00-6.00)
C_{max} (ng/mL)	490 (61)	672 (58)
AUC(0-4) (ng•h/mL)	1150 (54)	1620 (56)

[a] Median (range)

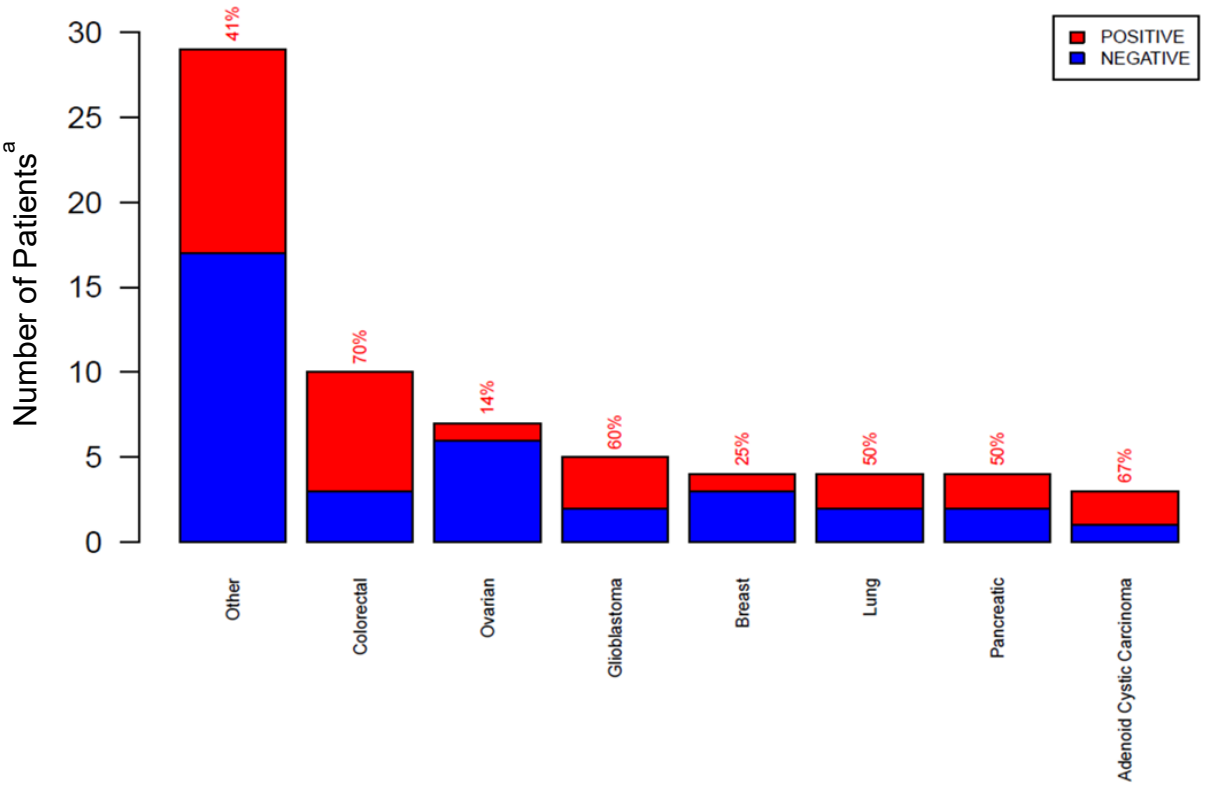
Supplementary Figure 1. Dose schedule of LY3039478



Supplementary Figure 2. Effect of LY3039478 on GI tract

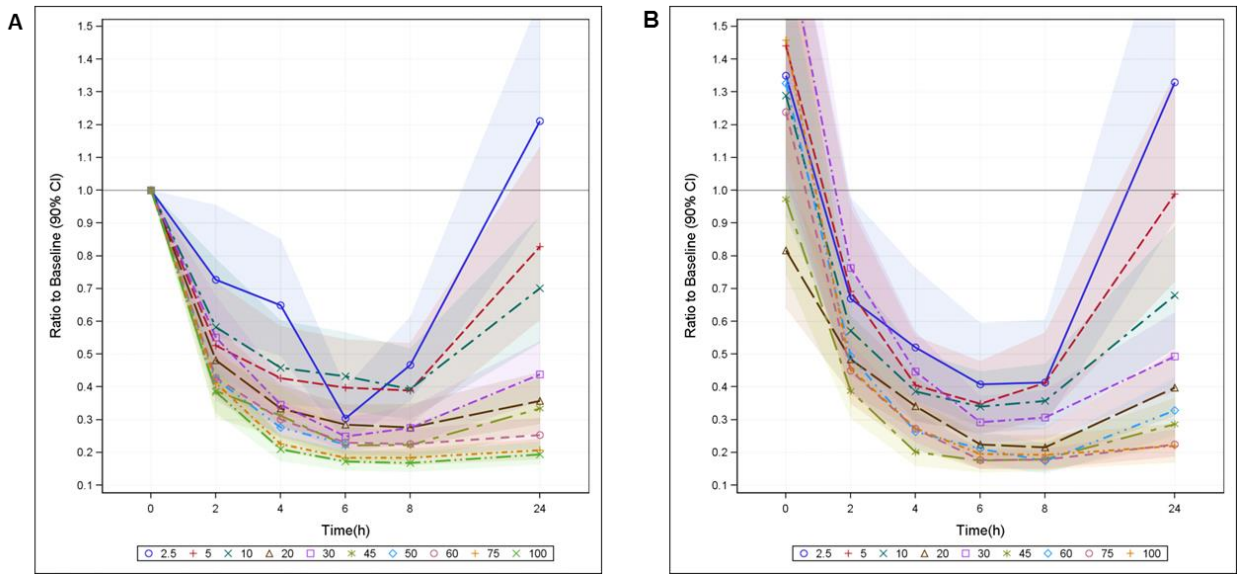


Supplementary Figure 3. NICD Activation of Notch Receptor 1. The percentage of each cancer category staining positive for Notch 1 NICD is presented



[a]Population in part B was selected for notch alterations

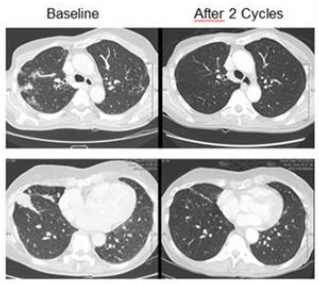
Supplementary Figure 4. Fold Change from Baseline Plasma Amyloid-Beta with corresponding 90% confidence interval A. Day 1. B. Day 22



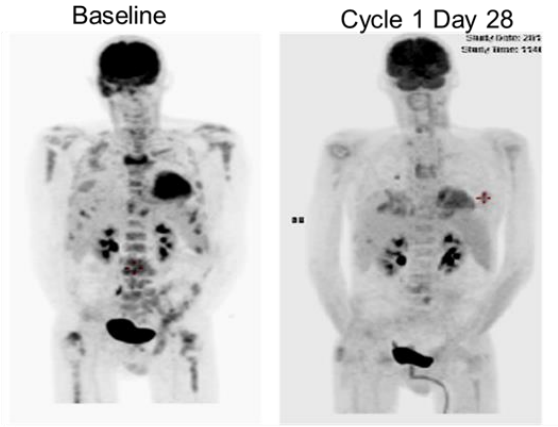
Note: Axis range truncated for visual purpose

Supplementary Figure 5. Patient Scans

72-year-old female patient with infiltrating ductal breast carcinoma



33-year-old male patient with adenoid cystic carcinoma



59-year-old female patient with abdomen (non-GIST) leiomyosarcoma